

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference NEREUS .091VP	FOR FURTHER ACTION		see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US2005/014846	International filing date (day/month/year) 29/04/2005	(Earliest) Priority Date (day/month/year) 30/04/2004	
Applicant NERUES PHARMACEUTICALS, INC			

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the language, the international search was carried out on the basis of:



the international application in the language in which it was filed



a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

- b. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☐ Certain claims were found unsearchable (See Box No. II)

3. ☒ Unity of Invention is lacking (see Box No. III)

4. With regard to the title,



the text is approved as submitted by the applicant



the text has been established by this Authority to read as follows:

5. With regard to the abstract,



the text is approved as submitted by the applicant



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the drawings,

- a. the figure of the drawings to be published with the abstract is Figure No. _____



as suggested by the applicant



as selected by this Authority, because the applicant failed to suggest a figure



as selected by this Authority, because this figure better characterizes the invention

- b. ☐ none of the figures is to be published with the abstract

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Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

see annex

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-2, 5-7, 9-12, 18-19, 21-24, 28-30, 37-51, 53-64 (all part)

related to the compounds of formula I in which R3 is a halogen, their compositions and the use thereof

2. claims: 1 (part), 4, 5 -12 (part), 13, 14, 16, 17, 18 -19 (part), 20, 21-30 (part), 31-33, 37-51 (part), 52, 53-64 (part)

related to the compounds of formula I in which R3 is a methyl and R2 comprises at least a cycle, their compositions and the use thereof

3. claims: 1-2 (part), 3, 5 -10 (part), 21-27 (part), 37-51 (part), 53-64 (part)

related to the compounds of formula I in which R3 is a methyl and R2 does not comprise a cycle, their compositions and the use thereof

4. claims: 1-2, 5 -7, 9-12, 18-19, 21-24 , 28-30, 37-51, 53-64 (all part)

related to the compounds of formula I in which R3 is a C2-C24 alkyl, unsaturated C2-C24 alkenyl, unsaturated C2-C24, acyl, acyloxy, alkyloxycarbonyloxy, aryloxycarbonyloxy, cycloalkyl, cycloalkenyl, alkoxy, cycloalkoxy, aryl, heteroaryl, arylalkoxy carbonyl, alkoxy carbonylacyl, phenyl, cycloalkylacyl, alkylthio, arylthio, carboxy and halogenated alkyl including polyhalogenated alkyl, hydroxy, oxysulfonyl, amino, aminocarbonyl, aminocarbonyloxy, nitro, azido, cyano their compositions and the use thereof.

5. claims: 34-36

related to the compounds of formula VI, their compositions and the use thereof

INTERNATIONAL SEARCH REPORT

International application No

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A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D491/04 C07D207/12 C07F5/02 A61K31/407

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D C07F A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EP0-Internal, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>FELING ROBERT H ET AL: "Salinosporamide A: a highly cytotoxic proteasome inhibitor from a novel microbial source, a marine bacterium of the new genus salinospora" ANGEHANTDE CHEMIE. INTERNATIONAL EDITION, WILEY VCH VERLAG, WEINHEIM, DE, vol. 42, no. 3, 20 January 2003 (2003-01-20), pages 355-357, XP002304842 ISSN: 1433-7851 page 355; compound 1</p> <p>-----</p>	1-64
A	<p>WO 99/15183 A (PROSCRIPT INC; ELLIOT, PETER; ADAMS, JULIAN; PLAMONDON, LOUIS) 1 April 1999 (1999-04-01) page 1, lines 16,17 page 3, lines 3,4 page 18; compounds 3A-E</p> <p>-----</p>	1-64

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may show doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document relating to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"S" document member of the same patent family

Date of the actual completion of the international search

25 September 2006

Date of mailing of the international search report

29.12.2006

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentean 2
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Authorized officer

Jeanjean, Fabien

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2005/014846

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9915183	A	01-04-1999	AU 9580098 A	12-04-1999
			CA 2304622 A1	01-04-1999
			EP 1017398 A1	12-07-2000
			JP 2001517631 T	09-10-2001

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA220

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2005/014846

International filing date (day/month/year)
29.04.2005

Priority date (day/month/year)
30.04.2004

International Patent Classification (IPC) or both national classification and IPC
INV. C07D491/04 C07D207/12 C07F5/02 A61K31/07

Applicant
NERUES PHARMACEUTICALS, INC

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1 bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA220.

3. For further details, see notes to Form PCT/ISA220.

Name and mailing address of the ISA:



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Fax: +49 89 2399 - 4465

Date of completion of
this opinion

see form
PCT/ISA210

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/014846

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ on paper
 - ☐ in electronic form
 - c. time of filing/furnishing:
 - ☐ contained in the International application as filed.
 - ☐ filed together with the international application in electronic form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

- ☐ the entire international application
- ☒ claims Nos. 1-2 (part), 3-4, 5-7 (part), 8, 9-12 (part), 13-17, 18-19 (part), 20, 21-24 (part), 25-27, 28-30 (part), 31-36, 37-38 (part), 39-51 (industrial applicability), 52, 53-61 (industrial applicability), 62-63 (part), 64 (industrial applicability)

because:

- ☒ the said international application, or the said claims Nos. 39-51, 53-61, 64 (industrial applicability) relate to the following subject matter which does not require an international search (specify):

see separate sheet

- ☐ the description, claims or drawings (*Indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (specify):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (specify):
- ☒ no international search report has been established for the whole application or for said claims Nos. 1-2 (part), 3-4, 5-7 (part), 8, 9-12 (part), 13-17, 18-19 (part), 20, 21-24 (part), 25-27, 28-30 (part), 31-36, 37-51 (part), 52, 53-64 (part),
- ☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:
- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13ter.1(a) or (b).
- ☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See Supplemental Box for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

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Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:
- ☐ paid additional fees
 - ☐ paid additional fees under protest and, where applicable, the protest fee
 - ☐ paid additional fees under protest but the applicable protest fee was not paid
 - ☒ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☐ all parts.
 - ☒ the parts relating to claims Nos. 1-2, 5-7, 9-12, 18-19, 21-24, 28-30, 37-51, 53-64 (all part)

Box No. V Reasoned statement under Rule 43b fs.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-2, 5-7, 9-12, 18-19, 21-24, 28-30, 37-51, 53-64 (all part)
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-2, 5-7, 9-12, 18-19, 21-24, 28-30, 37-51, 53-64 (all part)
Industrial applicability (IA)	Yes: Claims	1-2, 5-7, 9-12, 18-19, 21-24, 28-30, 37-38, 62-63 (all part)
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item III.

Claims 39 to 51, 53 to 61, 64 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item IV.

The separate inventions are:

This Authority considers that there are 5 inventions covered by the claims indicated as follows:

I: Claims 1 to 2, 5 to 7, 9 to 12, 18 to 19, 21 to 24, 28 to 30, 37 to 51, 53 to 64 (all part) related to the compounds of formula I in which R_3 is a halogen, their compositions and the use thereof

II: Claims 1 (part), 4, 5 to 12 (part), 13, 14, 16, 17, 18 to 19 (part), 20, 21 to 30 (part), 31 to 33, 37 to 51 (part), 52, 53 to 64 (part) related to the compounds of formula I in which R_3 is a methyl and R_2 comprises at least a cycle, their compositions and the use thereof

III: Claims 1 to 2 (part), 3, 5 to 10 (part), 21 to 27 (part), 37 to 51 (part), 53 to 64 (part), related to the compounds of formula I in which R_3 is a methyl and R_2 does not comprise a cycle, their compositions and the use thereof

IV: Claims 1 to 2, 5 to 7, 9 to 12, 18 to 19, 21 to 24, 28 to 30, 37 to 51, 53 to 64 (all part) related to the compounds of formula I in which R_3 is a C_2 - C_{24} alkyl, unsaturated C_2 - C_{24} alkenyl, unsaturated C_2 - C_{24} acyl, acyloxy, alkyloxycarbonyloxy, aryloxycarbonyloxy, cycloalkyl, cycloalkenyl, alkoxy, cycloalkoxy, aryl, heteroaryl, arylalkoxy carbonyl, alkoxy carbonylacyl, phenyl, cycloalkylacyl, alkylthio, arylthio, carboxy and halogenated alkyl including polyhalogenated alkyl, hydroxy, oxysulfonyl, amino, aminocarbonyl, aminocarbonyloxy, nitro, azido, cyano their compositions and the use thereof.

V: Claims 34 to 36 related to the compounds of formula VI, their compositions and the use thereof

The reasons for which the inventions are not so linked as to form a single general inventive concept, as required by Rule 13.1 PCT, are as follows:

The closest prior art for the present application is represented by D1 disclosing the salinosporamide A which exhibits potent cancer cell cytotoxicity and appears to be a 20S proteasome inhibitor (see p. 355, scheme 1). This compound is excluded by the applicant with a proviso. According to D2 the 20S complex is the proteolytic core of a 26S complex that degrades or processes ubiquitin-conjugated proteins (see p. 1, l. 16 to 17)). Furthermore proteasome inhibitors block I κ B- α degradation and activation of Nf- κ B (see p. 3, l 3 to 4).

The technical problem underlying the present claims is seen as the provision of further compounds for the treatment of cancer and other proteasome or Nf- κ B related disorders.

In view of the above mentioned compounds of D1, the different groups of compounds related to the above-mentioned inventions do not share a common special technical feature as required by rule 13.2 PCT. Therefore the application lacks of unity of invention (Rule 13.1 PCT).

Only the first invention has been searched.

Re Item V.

Reasoned statement with regard to novelty, inventive step or industrial applicability on the first invention; citations and explanations supporting such statement

1 Reference is made to the following document:

- D1 : "Salinosporamide A: A Highly Cytotoxic Proteasome Inhibitor from a Novel Microbial Source, a Marine Bacterium of the New Genus *Salinospora*", Feling R. H., Buchanan G. O., Mincer T. J., Kauffman C. A., Jensen, P. R., Fenical W., *Angewandte Chemie International Edition*, **2003**, 42, 3, 355-357
D2 : WO9915183

2 Novelty

2.1 The subject-matter of claims 1 to 2, 5 to 7, 9 to 12, 18 to 19, 21 to 24, 28 to 30, 37 to 51, 53 to 64 (all part) appears to be new in the sense of Article 33(2) PCT.

2.2 The document D1 discloses (the references in parentheses applying to this document): the salinosporamide A (p. 355, scheme 1, compound 1) which is excluded with a proviso by the applicant from the scope of formula I.
The compound of formula I of claim 1 and of the dependent claims 2, 5 to 7, 9 to 12, 18 to 19, 21 to 24, 28 to 30 appears to be new vis-à-vis D1.
The same reasoning applies, mutatis mutandis, to the subject-matter of the corresponding claims 37 to 51, 53 to 64 which therefore are also considered new vis-à-vis D1.

2.3 The document D2 discloses (the references in parentheses applying to this document): the compounds 3a to 3e (p. 18, scheme 2). The compounds of the present application differ in that R₃ cannot represent a hydrogen.
The compound of formula I of claim 1 and of the dependent claims 2, 5 to 7, 9 to 12, 18 to 19, 21 to 24, 28 to 30 appears to be new vis-à-vis D2.
The same reasoning applies, mutatis mutandis, to the subject-matter of the corresponding claims 37 to 51, 53 to 64 which therefore are also considered new vis-à-vis D2.

3 Inventive step

3.1 The present application appears to not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1 to 2, 5 to 7, 9 to 12, 18 to 19, 21 to 24, 28 to 30, 37 to 51, 53 to 64 (all part) does not involve an inventive step in the sense of Article 33(3) PCT.

3.2 The document D1 is regarded as being the closest prior art to the subject-matter of claim 1, and discloses (the references in parentheses applying to this document): salinosporamide A (p. 355, cpd. 1, scheme 1) which exhibits potent cancer cell cytotoxicity and appears to exert its cytotoxic effects through inhibition of the 20S proteasome (p. 355). The compounds of the first invention differ in that R₃ is a halogen instead of a methyl.

The problem to be solved by the present invention may therefore be regarded as the provision of further compounds inhibitor of proteasome for the treatment of cancer. There are no examples in the description of compounds of the first invention showing an inhibition of proteasome. It seems that the compounds of the first invention do not solve the problem above mentioned. An inventive step cannot therefore be acknowledged for the compounds of claim 1 and the dependent claims 2, 5 to 7, 9 to 12, 18 to 19, 21 to 24, 28 to 30.

The same reasoning applies, *mutatis mutandis*, to the subject-matter of the corresponding claims 37 to 51, 53 to 64 which therefore are also considered not inventive.

Remarks

- 1 The term "prodrug" used in claims 1, 5, 25, 31, 39, 44, 46, 47, 50, 53, 60 to 63 is considered unclear. The person skilled in the art is left to an undue burden when he has to decide which compounds are encompassed by the term prodrug.
- 2 The term "variant" used in claims 1, 5, 25 and 31 is vague and unclear and leaves the reader in doubt as to the meaning of the technical feature to which it refers, thereby rendering the definition of the subject-matter of said claim/s unclear, Article 6 PCT.
- 3 There is an obvious error in claims 36, 37, 39, 44, 46, 47, 48, and 50 wherein the claimed pharmaceutical composition (or methods) comprises (or use) a compound of claims 46 and 49 (related to methods).
- 4 The terms "alkyl", "alkenyl", "alkoxy" are defined in the description (see p. 72, par. 298) as a "unsubstituted or substituted" hydrocarbon or ether. This definition does not correspond to the common meaning given for these terms in organic chemistry. This inconsistency between the description and the claims has to be removed.
- 5 The vague and imprecise statement "spirit of invention" in the description on page 156 (par 510 and 511) implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity (Article 6 PCT) when used to interpret them.
- 6 The statement "the invention illustratively described herein suitably can be

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

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practised in the absence of any element or elements, limitation or limitations which is not specifically disclosed herein" lets the impression that not all the technical features for performing the invention are disclosed. It seems therefore that there is a lack of disclosure of the present invention.

7 Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document D1 is not mentioned in the description, nor are this document identified therein.